stirring a solution of 14.9 g of $NaHSO_3$, 251 ml of H_2O, and 160 ml of pyridine. After 15 min the solution was extracted twice with $CHCl_3$. The $CHCl_3$ extract was dried ($MgSO_4$) and distilled to dryness. Slow evaporation and trituration of an $Et_2O-C_6H_{14}$ solution of the residue gave 7.45 g of crude diol: mp 110–125°; nmr maxima at 58 (C-13 Me) and 68 and 74.5 (C-21 Me) cps. A solution of 6.6 g of the crude diol **3a** in 100 ml of DMF was added with stirring to a cold solution of 35.6 ml of 8 N $CrO_3-H_2SO_4$, 4.7 g of $MnCl_2$, and 78 ml of DMF. The solution was stirred for 2.5 hr at 20° and then added while stirring vigorously, to 2.2 l. of ice and H_2O. The crude product which was collected by filtration and dried, weighed 5.3 g. The crude product was dissolved in C_6H_6 and purified by column chromatography on 450 g of silica gel (Davison 60–200 mesh). Elution of the column with C_6H_6–EtOAc (9:1) gave 1.3 g of **3b**, mp 147–148°. Crystallization of the crude product (Et_2O) gave an analytical sample: mp 149–151°; nmr maxima at 53 (C-13 methyl), 110 and 137 (9H, C-3, C-11, and C-20 acetyl) cps. *Anal.* ($C_{24}H_{30}O_6$) C, H.

3,11β-Trihydroxy-19-norpregna-1,3,5(10)-trien-20-one (3c).—To a solution of 900 mg of crude **3b** in 100 ml of MeOH was added with stirring a solution of 500 mg of KOH in 20 ml of 50% aqueous MeOH. The solution was warmed and 50 ml of H_2O was added. The MeOH was removed by distillation and the solution was refluxed under N_2 for 5 hr, cooled, and acidified at 0° with AcOH. The product, which was collected by filtration, washed (H_2O), and dried, weighed 620 mg. Crystallization of the crude product (Me_2CO and hexane) gave an analytical sample: mp 237–240°; λ_{max} (KBr) 2.82, 2.99, 5.82, and 6.17 μ. The ORD curve of **3c** in MeOH exhibited a broad peak at 330 mμ (Φ 1122) and a trough at 295 mμ (Φ 900). *Anal.* ($C_{20}H_{26}O_4$) C, H.

Barbiturates. Structural Comparisons. I. Amobarbital, Methylamobarbital, and Butethal[1]

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Recently a quantitative study has been made concerning the structure–activity relationships of the barbiturates.[2,3] It has been suggested that the partition coefficients and the rate of metabolism play an important role in the duration of action and potency of the barbiturates.[3] With reference to the metabolic inactivation of barbiturates, it has been shown that the ω − 1 carbon of the side chain of barbiturates undergoes preferential oxidation in many cases. In several barbiturates studied,[4] the ω − 1 carbon turned out to be the β- or γ-carbon atom. In order to differentiate between the γ carbon or ω − 1 carbon as to the susceptibility toward oxidation, Maynert[5] studied the metabolism of 5-ethyl-5-*n*-hexylbarbituric acid in dogs and found the ω − 1 carbon and not the γ carbon most susceptible to metabolic oxidation.

With this in mind, it was decided to study compounds without C–H bonds at the ω − 1 carbon. If the ω − 1 carbon does not possess a C–H bond, that carbon will not be susceptible to oxidation and

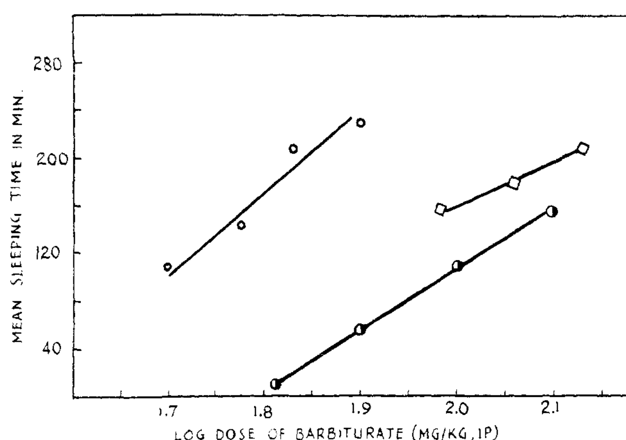
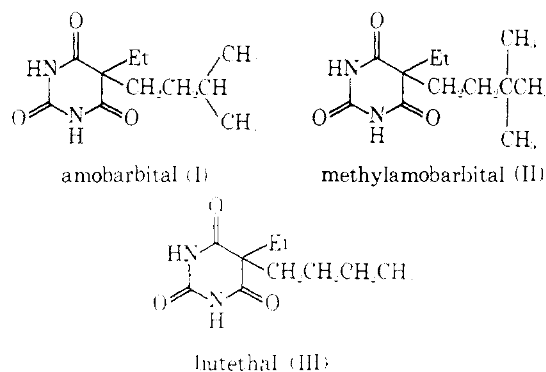


Figure 1.—Log dose-response (duration of action) curves of amobarbital (AMB·Na) (◐—◐), butethal (BUT·Na) (◇—◇), and methylamobarbital (CH_3AMB) (O—O) in male mice. Each point represents the value obtained from ten animals.

one would expect a longer acting and more potent compound. The compounds chosen for the first comparison were 5-ethyl-5-(3-methylbutyl)barbituric acid (amobarbital, I), 5-ethyl-5-(3,3-dimethylbutyl)barbituric acid (methylamobarbital, II), and 5-ethyl-5-*n*-butylbarbituric acid (butethal, III). Comparison of the substituents on the ω − 1 carbon for I and II should give a good estimate of the difference between a very easily oxidized ω − 1 C–H bond as in I (forms a tertiary free radical)[6] against a carbon containing no



ω − 1 C–H bonds for oxidation as in II. The pharmacological studies performed show that II is a more potent and a longer acting compound than I or butethal.

Pharmacological Studies.—Figure 1 shows the relationship between dose and the duration of action of amobarbital, butethal, and methylamobarbital in mice. It can be readily seen that amobarbital is shorter acting than methylamobarbital. Comparisons at 120 min show methylamobarbital to be 1.9 times as active as amobarbital when compared on an equimolar basis.

In order to relate this difference in activity to the differences in metabolic inactivation, the oxidative enzymes (liver) were blocked by using β-diethylaminoethyl diphenylpropylacetate and iproniazid.[7,8] The results are shown in Figures 2 and 3. Figure 2

(1) This work was supported by Grant FR-05455 from the National Institutes of Health.
(2) C. Hansch and S. M. Anderson, *J. Med. Chem.*, **10**, 745 (1967).
(3) C. Hansch, A. R. Steward, S. M. Anderson, and D. Bentley, *ibid.*, **11**, 1 (1968).
(4) (a) E. W. Maynert and J. M. Dawson, *J. Biol. Chem.*, **195**, 389 (1952); (b) E. W. Maynert, *ibid.*, **195**, 397 (1952); (c) *ibid.*, **195**, 403 (1952).
(5) E. W. Maynert, *J. Pharmacol. Exptl. Therap.*, **150**, 476 (1965).
(6) Amobarbital can be hydroxylated at the ω-1 carbon atom by chromic acid oxidation under very mild conditions; see ref 4b.
(7) J. R. Cooper, J. Axelrod, and B. B. Brodie, *J. Pharmacol. Exptl. Therap.*, **112**, 55 (1954).
(8) J. R. Fouts and B. B. Brodie, *ibid.*, **116**, 480 (1956).

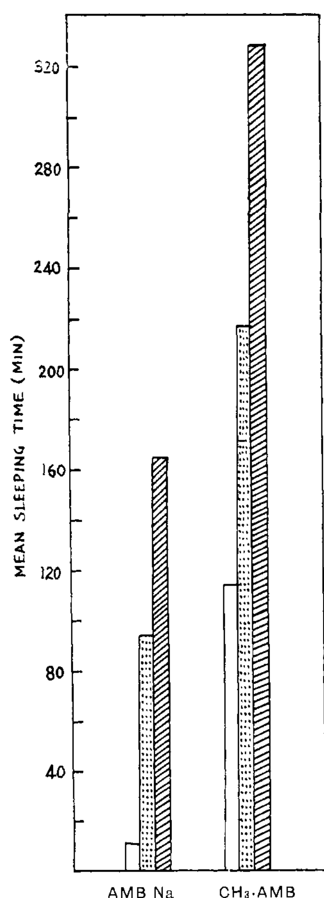


Figure 2.—Effect of β-diethylaminoethyl diphenylpropylacetate (SKF-525A) and iproniazide on the duration of action of equimolar doses (0.28 mmole/kg ip) of amobarbital (AMB·Na) (70 mg/kg) and methylamobarbital (CH_3AMB) (67.5 mg/kg) in male mice. β-Diethylaminoethyl diphenylpropylacetate (10 mg/kg ip) (▧) was given 60 min prior to and iproniazide phosphate (100 mg/kg ip) (▤) 30 min prior to the administration of barbiturates. Control animals received saline (5 ml/kg ip) (□). Each group consisted of ten animals.

shows that inhibition of these enzyme systems potentiated the duration of equimolar doses of amobarbital and methylamobarbital. Comparison on a per cent basis shows that the response to amobarbital was potentiated 8 and 14 times and methylamobarbital only 2 and 3 times. This is in line with the fact that the drugs which are metabolized at a slower rate will be affected less if the activity of the inactivating enzyme(s) is altered, either inhibited or increased. These results can then be interpreted to indicate that methylamobarbital is metabolized to a lesser degree than amobarbital due to the fact that the preferential site of oxidation is blocked by methylation.

The relative potencies (in terms of AD_{50}) of amobarbital, methylamobarbital, and butethal are shown in Figure 4. Methylamobarbital is 1.8 times as potent as butethal, whereas amobarbital is 1.3 times as potent as butethal when compared on an equimolar basis. It can be said that the onset of action of barbiturates is related to partition coefficientes since the potencies of methylamobarbital, amobarbital, and butethal increase (Figure 4) with increasing partition coefficients. However, when one looks at duration of action (Figure 1), butethal appears to be longer acting than amobarbital per unit dosage which is opposite to the potency relationship above. Butethal may be longer acting

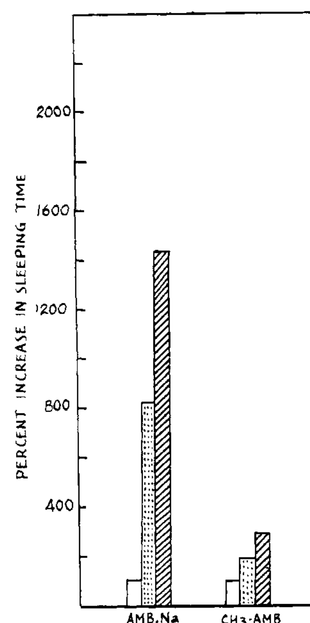


Figure 3.—Effect of β-diethylaminoethyl diphenylpropylacetate and iproniazide on the duration of action of equimolar doses (0.28 mmole/kg ip) of amobarbital (AMB·Na) (70 mg/kg) and methylamobarbital (CH_3AMB) (67.5 mg/kg) in male mice. The data are compared on a per cent basis. β-Diethylaminoethyl diphenylpropylacetate (10 mg/kg ip) (▧) was given 60 min prior to and iproniazide phosphate (100 mg/kg ip) (▤) 30 min prior to the administration of barbiturates. Control animals received saline (5 ml/kg ip) (□). Each group consisted of ten animals.

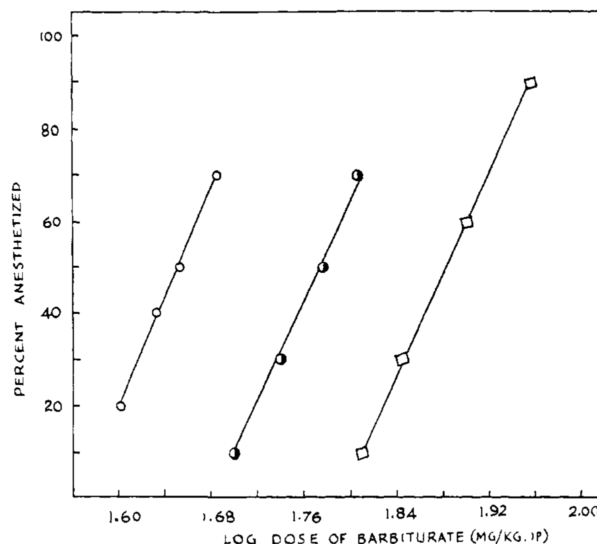


Figure 4.—Log dose–response (onset of action) curves of amobarbital (AMB·Na) (◐), butethal (BUT·Na) (◇), and methylamobarbital (CH_3AMB) (○) in male mice. Each point represents the value obtained from ten animals. AD_{50}'s (anesthetic dose for 50% of the animals) in mmole were CH_3AMB, 0.185; AMB, 0.240; BUT, 0.330.

than amobarbital because of its lower log P value and because it does not contain a tertiary $\omega - 1$ hydrogen.

One can explain these results by correlating potency (onset of action) with the partition coefficient as shown in the past,[2,3] whereas duration of action is more dependent upon the rate of metabolism and not entirely on the partition coefficients.

In order to determine the importance of metabolism with respect to $\omega - 1$ oxidation we are now studying longer chain derivatives and are synthesizing other compounds with the $\omega - 1$ carbon atom blocked by various substituents. Studies on the direct measurements of metabolsim by hepatic microsomes have also been initiated.

Experimental Section

5-Ethyl-5-(3,3-dimethylbutyl)barbituric acid (VII) was synthesized as shown in the literature[9] except that 3,3-dimethylbutyl chloride was used instead of the bromide. The melting point was 191-193°. The X-ray structure of our synthetic compound has been recently accomplished.[10]

(9) F. C. Whitmore and M. A. Thorpo. U. S. Patent 2,161,212 (1939).
(10) B. Craven, Department of Crystallography, University of Pittsburgh, personal communication.

Structure–Activity Relationships of Ethylenimines. VIII. Optically Active Methyl-Substituted Ethylenimines[1]

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The reaction of butadiene monoxide and propylenimine gives a 70:30 mixture of 1-(2-methyl-1-aziridinyl)-3-buten-2-ol and 2-(2-methyl-1-aziridinyl)-3-buten-1-ol.[2] Interestingly, the product mixtures obtained from D-propylenimine and L-propylenimine showed different activities against Adenocarcinoma 755, the L mixture being the more active. Although this difference in activity was suggestive of a relationship between biological activity and the absolute configuration of a substituted carbon on the aziridine ring, such an interpretation was considered tenuous because the products were not pure enantiomers.

In order to make possible more suitable examination of the relationship between biological activity and the absolute configuration of a substituted carbon on the aziridine ring, we prepared 2,5-bis(D-2-methylaziridinyl)-*p*-benzoquinone (D-I), tris(D-2-methyl-1-aziridinyl)phosphine sulfide (D-II), 2,4,6-tris(D-2-methyl-1-aziridinyl)-*s*-triazine (D-III), and their L enantiomers (L-I–III). Syntheses were accomplished using the appropriate D- or L-propylenimine[2] and methods similar to these described for preparation of the racemic analogs.[3,4] Preliminary screening data, obtained by the Cancer Chemotherapy National Service Center, are summarized in Table I.

Table I
Antitumor Activity[a]

Compd	Test system	Control no.	Dose,[b] mg/kg	Survivors	Wt dif, g, T − C	T/C[c]
D-I[d,e]	WA	329	3.50	6/6[f]	−31	0.2/7.0
	WA	329	1.70	5/6	4	4.9/7.0
	WA	329	0.80	6/6	−7	5.7/7.0
L-I[d,g]	WA	331	1.25	6/6	−8	3.7/8.0
	WA	331	0.62	6/6	−5	8.6/8.0
	WA	331	0.31	6/6	−4	6.2/8.0
D-II[h]	DL	256	12.0	4/6	−19	12.5/13.5
	DL	256	6.00	6/6[i]	−6	30.0/13.5
	DL	256	3.00	6/6	−5	20.0/13.5
	DL	256	1.50	6/6	−3	16.0/13.5
D-III[j-l]	WA	68	1.20	6/6	−17	0.0/10.0
	WA	68	0.60	6/6	−7	0.0/10.0
	WA	68	0.30	6/6	−19	5.4/10.0
	WA	68	0.15	6/6	7	9.0/10.0
	WA	74	0.300	6/6	0	3.3/7.9
	WA	74	0.150[m]	6/6	2	5.3/7.9
	WA	87	1.20[n]	6/6	−16	0.0/8.8
	WA	87	0.60[n]	6/6	−5	0.0/8.8
	WA	87	0.30[n]	6/6	−9	0.7/8.8
	WA	87	0.15[n]	6/6	4	3.7/8.8
	WA	87	0.08[n]	6/6	3	4.8/8.8
L-III[j,l]	WA	68	3.75	5/6	−34	0.0/10.0
	WA	68	1.87	6/6	−25	0.0/10.0
	WA	68	0.94	6/6	−22	9.1/10.0
	WA	68	0.47	6/6	2	3.9/10.0
	WA	74	0.94	6/6	−6	0.0/7.9
	WA	74	0.47	6/6	−26	1.3/7.9
	WA	74	0.24	6/6	−6	5.6/7.9
	WA	74	0.12	6/6	9	5.8/7.9
	WA	87	3.75[n]	4/6	−44	0.0/8.8
	WA	87	1.87[n]	6/6	−27	0.0/8.8
	WA	87	0.94[n]	6/6	−16	0.0/8.8
	WA	87	0.47[n]	6/6	−16	0.0/8.8
	WA	87	0.24[n]	6/6	−4	2.8/8.8
	WA	94	0.47[n]	7/7	−11	2.7/8.8
	WA	94	0.24[m,n]	7/7	−1	4.8/8.8

[a] See *Cancer Chemotherapy Rept.*, **25**, 1, 10 (1962). [b] Unless otherwise noted, the vehicle was carboxymethylcellulose, and the route was intraperitoneal. [c] For Walker 256 (WA) test system: tumor weight in grams; for Dunning leukemia (solid) (DL) test system: survival time in days. [d] In tests using KB cells with control numbers 343, 349, and 164 (two different screeners), D-I had ED_{50}'s of <1.0, 0.40 (slope = −0.46), and <0.25 μg/ml, respectively, and L-I had ED_{50}'s of <1.0, 0.36 (slope = −0.45), and 0.23 (slope = −0.78) μg/ml, respectively. [e] Toxic at a dose level of 7.10 mg/kg. [f] Four cures. [g] Toxic at a dose level of 2.50 mg/kg. [h] D-II and L-II, at dose levels of 6.00–48.0 and 3.75–400 mg/kg, respectively, did not produce prolonged survival times when tested against lymphoid leukemia L1210 test system. [i] Six cures. [j] From tumor inhibition *vs.* dosage plots of these data, T/C 0.10 were estimated for D- and L-III as *ca.* 0.5 and 1.4 mg/kg/day, respectively; the approximate 95% confidence limits were 0.2–1.2 and 0.4–4.8 mg/kg/day, respectively. [k] From a tumor inhibition *vs.* dosage plot of similar data (control numbers 36, 87, 94, 103, and 110) for 2,4,6-tris(2-methyl-1-aziridinyl)-*s*-triazine prepared with racemic propylenimine, T/C 0.10 was estimated as *ca.* 12.5 mg/kg/day, with approximate 95% confidence limits of 1.2–12 mg/kg/day. [l] Preliminary LD_{50}'s for D-III, L-III, and III prepared from racemic propylenimine are 1.2, 3.8, and 12.5 mg/kg/day. [m] Inactive at lower dose levels in this series. [n] The vehicle was saline.

Although the paucity of the data does not allow any conclusion regarding the relationship of activity and the absolute configuration of the substituted carbon on the aziridine ring, D-III appears to be more active

(1) (a) Part VII: A. T. Bottini, B. F. Dowden, and R. L. VanEtten, *J. Am. Chem. Soc.*, **87**, 3250 (1965). (b) Supported in part by Grant No. CA-05528 from the National Cancer Institute of the Public Health Service.
(2) A. T. Bottini and V. Dev, *J. Med. Pharm. Chem.*, **5**, 925 (1962).
(3) (a) W. Gauss, S. Petersen, G. Domagk, and C. Hackmann, German Patent 967,344 (Nov 7, 1957); *Chem. Abstr.*, **53**, 13173 (1959); (b) E. Kuh and F. R. Seeger, U. S. Patent 2,670,347 (Feb 23, 1954); *Chem. Abstr.*, **49**, 2181 (1955); (c) F. C. Schaefer, *J. Am. Chem. Soc.*, **77**, 5928 (1955).
(4) Note that use of racemic propylenimine instead of optically pure propylenimine in any of these syntheses gives a mixture of diastereomers. For example, in the absence of asymmetric induction, the reaction of thiophosphoryl chloride with racemic propylenimine will give a 3:1 mixture of the DDL,LLD and DDD,LLL diastereomers.